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de Geus, E.J.C.

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Genetic Pleiotropy in Depression and Coronary Artery Disease

Strong evidence has accrued over the past decade that depressive symptoms predict future cardiac disease (1,2). The link is not "merely" significant; the effect size is sufficiently high to suggest that it is also relevant. Depression is estimated to confer a relative risk between 1.5 and 2.0 for the onset of coronary artery disease (CAD) in healthy individuals, whereas depression in patients with existing CAD confers a relative risk between 1.5 and 2.5 for new morbidity and mortality (3). Here we had a link between psychosocial factors and somatic disease that could not be easily silenced by hard-core "psychosomatic medicine skeptics" (4). So we thought. Then things started to go awry. A large randomized controlled trial that targeted depressive symptoms and social isolation by behavioral therapy (ENRICHD) did not reduce the risk for myocardial reinfarction or mortality (5). This was bad news. First and foremost for those afflicted with CAD, because a novel therapeutic route to supplement usual care appeared to be shut off. The news was also bad for the field: strong prospective evidence for a link between psyche and soma will not necessarily materialize as a causal effect.

Explanations for the disappointing results abound (6), and secondary analyses may yet change our overall perception of this trial (7,8). In this issue of *Psychosomatic Medicine*, McCaffery and colleagues (9) urge us to be willing to entertain an alternative explanation for the current state of affairs. We need to remind ourselves that prediction is nothing more than an association, in this case an association of a trait (depression) at wave 1 with another trait (coronary artery disease) at wave 2 of data collection. Remember that association does not equate with causation? Individual differences in some underlying dimension could affect susceptibility for depression at time 1 but simultaneously, and unrelated to its effects on depression, also affect the severity of CAD at time 2. This would give rise to a prospective link between depressive symptoms and CAD, but causal effects would flow forth from the underlying dimension only. McCaffery and colleagues propose that this underlying dimension is in part to be found in individual differences in genetic makeup.

The crucial concept is that of genetic pleiotropy, i.e., the finding that a single gene can influence variance in multiple and very diverse traits. For instance, variation in the gene coding for the 5-HT2A receptor might influence the ease by which the receptor is incorporated into the cell membrane. In the central nervous system, the increased receptor density may affect serotonergic neurotransmission and influence mood regulation. In peripheral tissues, the increased receptor density may enhance platelet aggregation and vasoconstriction. These central and peripheral effects of the 5-HT2A gene may be completely unconnected; they may just reflect the evolutionary mechanism that nature selects for a successful ligand-receptor system and re-employs whenever it sees fit.

The existence of genetic pleiotropy can be demonstrated by a twin study. Twins come in two flavors: monozygotic twins, who are genetically identical; and dizygotic twins, who share on average 50% of their genetic material (10). The crucial piece of information needed to detect pleiotropy is found in the cross-twin cross-trait correlations. If the depressive symptoms of a twin predict CAD in their co-twin, this can only be explained by an underlying factor that affects both depression and CAD and is shared by members of a family. If the prediction is about twice as strong in monozygotic twins than in dizygotic twins, this signals that the underlying factor is their shared genetic makeup. Exactly this result has been found (11), and 17% of variability in depressive symptoms and self-reported heart disease appears to be attributable to common genetic factors influencing both traits.

In twin studies, these genetic factors remain anonymous (the latent "G" factors in the often-used path diagrams); but when DNA has been collected, actual genes can be tested using genetic association analysis. McCaffery and colleagues review the current molecular genetic evidence for pleiotropy as a potential source of the association between CAD and depressive symptoms (10). In selecting genes, the authors have focused on inflammation and serotonergic cell-to-cell signaling as two potential pathways that could influence both affective state and cardiovascular functioning. A comprehensive list of candidate genes in these pathways is discussed, although by necessity constrained by our current knowledge of the human genome. From the listed candidate genes, the most convincing case is made for TNFA, IL1B, 5-HTT, 5-HT2A, and 5-HT2B because polymorphic variation within these genes has already been linked to both depression and CAD.

Taking the concept of pleiotropy to the extreme could mean that actively changing psychosocial risk would have little preventive value at all, since it would not change the subject's genotype. This is hard to digest. In defense of true causal effects driving the prospective link between depression and CAD outcome, one should point out that evidence for pleiotropy still does not exclude additional causal effects. All that is shown, by the reviewed twin and association studies alike, is that some genes may influence variance in both traits. This can mean one of four things: genes cause depression and depression causes CAD, genes cause CAD and CAD causes depression, genes cause depression *and* CAD but do so independently (true pleiotropy). Finally, in a fourth and most likely scenario, the previous three scenarios coexist. Some genes for CAD may act by causing

Address correspondence and reprint requests to Eco J. C. de Geus, PhD, Department of Biological Psychology, Vrije Universiteit, van der Boechorststraat 1, Amsterdam, NH 1081 BT Netherlands. E-mail: eco@psy.vu.nl

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depressive symptomatology (e.g., 5-HTT (12) or FKBP5 (13)) and through the chronic stress of depression worsen CAD prognosis (14); some genes may act directly on atherosclerosis (e.g., IL1B (15,16)) and the resulting vascular disease may influence the course of depression (17); still other genes may act to affect mood in the central nervous system but independently act on CHD risk in peripheral tissues like the heart and blood vessels (e.g., genes coding for adrenoceptors). All this is hypothetical, of course, but the important message conveyed by the review is that we can and should test such hypotheses.

I found the review to be exemplary in three ways. First, a series of candidate genes are listed that allow empirical interrogation of the new theoretical position that genetic pleiotropy may explain part of the link between depressive symptoms and CAD. Second, the paper was co-authored by pioneers in the depression/CAD link, who now dare question their previous conclusions. This open-mindedness refutes the sentiment that this field is unwilling to change theory when faced with unfavorable empirical evidence. Third, and most importantly, the review by McCaffery and colleagues shows that researchers with a firm base in psychosomatic medicine can successfully adopt genetic strategies and, most importantly, become beneficiaries of the Human Genome Project. DNA is just another tool to help us chart the pathways connecting body and mind. If we consider psychosomatic medicine to be a complex puzzle, then genes should simply be regarded as the edge pieces.

The edges are generally not a bad place to start assembling a puzzle.

ECO J. C. DE GEUS, PHD
From the Department of Biological Psychology & the Netherlands Twin Registry, Vrije Universiteit, Amsterdam, The Netherlands.

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